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Minireview

The diversity of globin-coupled sensors

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Abstract The recently discovered globin-coupled sensors (GCSs) are heme-containing two-domain transducers distinct from the PAS domain superfamily. We have identified an additional 22 GCSs with varying multi-domain C-terminal transmitters through a search of the complete and incomplete microbial genome datasets. The GCS superfamily is composed of two major subfamilies: the aerotactic and gene regulators. We postulate the existence of protoglobin in Archaea as the predecessor to the chimeric GCS.

Key words: Globin; Archaeon; Heme-based sensor; Globin-coupled sensor

1. Introduction

Homo- and heteromeric heme-based sensors are mediators of cellular responses to metabolic and environmental stimuli such as NO, CO and O_2 [1]. Changes in intracellular gas concentrations are sensed by a heme moiety and result in either aerotaxis or gene regulation. Presently, there are six known types of heme sensors: CooA, NPAS2, sGC, Dos and *Ax*PDEA1, FixL and HemAT. The HemATs, by homology, are the only aerotactic heme sensors combining globin and MCP signaling domains, whereas the remaining function in gene regulation, either by binding DNA directly, modulating a small metabolite 2nd messenger (cyclic mono- and di-NMPs), or directly interacting with a transcription factor or regulator.

CooA is a CO sensor that controls the transcription of CO-utilizing genes. Binding of CO to the heme domain of CooA homodimers modulates the DNA-binding C-terminal domain [2]. Neuronal PAS domain protein 2 (NPAS2) is expressed in mammalian brain tissue [3] and regulates transcription as a heterodimer with BMAL1 [4–6]. Dissociation of the NPAS2:BMAL1 heterodimer occurs upon CO binding to the NPAS2 monomer, effectively removing its DNA-binding, and hence, transcription capability [3]. The soluble guanylate cyclase (sGC) contains a heme-binding and guanylate cyclase domain. Binding of NO to the sGC heterodimer produces cGMP from GTP [7], whereby gene regulation ensues by the cGMP 2nd messenger. The direct oxygen sensor (Dos), first described in *Escherichia coli* [8], functions as a tetrameric phosphodiesterase (PDE) by converting cAMP to 5′-AMP while in the ferrous form, and is strongly inhibited by CO and NO ligands [9]. A1 from *Acetobacter xylinum* (*Ax*PDEA1) also functions as a PDE by linearizing cyclic bis(3′→5′)diguanylate, an allosteric activator of the bacterial cellulose synthase, to the ineffectual pGpG [10,11]. Both Dos and *Ax*PDEA1 possess similar heme-binding PAS domains fused to the PDE C-terminus, consisting of a GGDEF and EAL domain. Histidine kinase FixL binds heme at an N-terminal PAS domain and controls transcription of oxygen-sensitive genes by its response regulator, FixJ [13,14]. Phosphorylated FixJ acts as the transcriptional activator and permits transcription of the *fix* genes [15,16].

Heme-based aerotaxis transducers, the HemATs, possess a heme-binding globin domain and a signaling domain typical of methyl-accepting chemotaxis proteins (MCP) [17]. HemATs, originally discovered in the archaeon *Halobacterium salinarum* and the Firmicutes *Bacillus subtilis*, are members of the family of globin-coupled sensors (GCSs) [18,19]. Variance in the C-terminal transmitter domain indicates that not all GCSs are involved in aerotaxis. In this report, we further identify the diversity of these GCSs resulting from exhaustive searches of completed and in-progress microbial genomes. We also report their putative functions and categorize them in relation to other non-globin heme-based sensors and propose two possible evolutionary models of the GCS and globin.

2. Materials and methods

2.1. Genome and protein sequences

The following preliminary sequence data was obtained from the Institute for Genomic Research website: *Acidithiobacillus ferrooxidans*, *Bacillus anthracis*, *Bacillus cereus*, *Carboxydothermus hydrogenoformans*, and *Geobacter sulfurreducens*; DOE Joint Genome Institute: *Azotobacter vinelandii*, *Burkholderia fungorum*, *Geobacter metallireducens*, *Magnetococcus*, *Magnetospirillum magnetotacticum*, *Rhodobacter sphaeroides*, *Rhodospirillum rubrum*, and *Novosphingobium aromaticivorans*; National Center for Biotechnology Information: *Escherichia coli* O157 H7, *Halobacterium salinarum*, *Agrobacterium tumefaciens*, *Caulobacter crescentus*, *Bacillus halodurans*, *Bacillus subtilis*, *Vibrio vulnificus*, and *Shigella flexneri*; the *Bordetella pertussis*, *Bordetella parapertussis*, and *Bordetella bronchiseptica* sequence data was produced by the *Bordetella pertussis* Sequencing Group at the Sanger Institute and can

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be obtained from ftp://ftp.sanger.ac.uk/pub/pathogens/bp/. At present, five genomes are incompletely sequenced and therefore accession numbers are not available for those proteins (see Table 1 for details).

2.2. Multiple alignments and secondary structure

All sequences were aligned in a two-stage process. Multiple alignments in ClustalX v1.8 [20] were followed by manual adjustment in DNAStar's MegAlign. At this stage, globin crystal structures (*E. coli* HMP, PDB ID: 1GVH; *Vitreoscilla stercoraria* Hb, PDB ID: 1VHB; *Ralstonia eutropha* FHb, PDB ID: 1CQX; *Chlamydomonas eugametos* trHb, PDB ID: 1DLY; *Paramecium caudatum* trHb, PDB ID: 1DLW; HemAT-*Bs*, PDB ID: 1OR6) and Jnet [21] secondary structure predictions were used as guides to produce the finished alignments in Fig. 1A.

2.3. Protein domain detection and analyses

Protein sequences were analyzed with the Pfam (http://pfam.wustl.edu/), SMART (http://smart.embl-heidelberg.de/), and SCOP (http://scop.berkeley.edu/) datasets and domain descriptions were taken from the InterPro database (http://

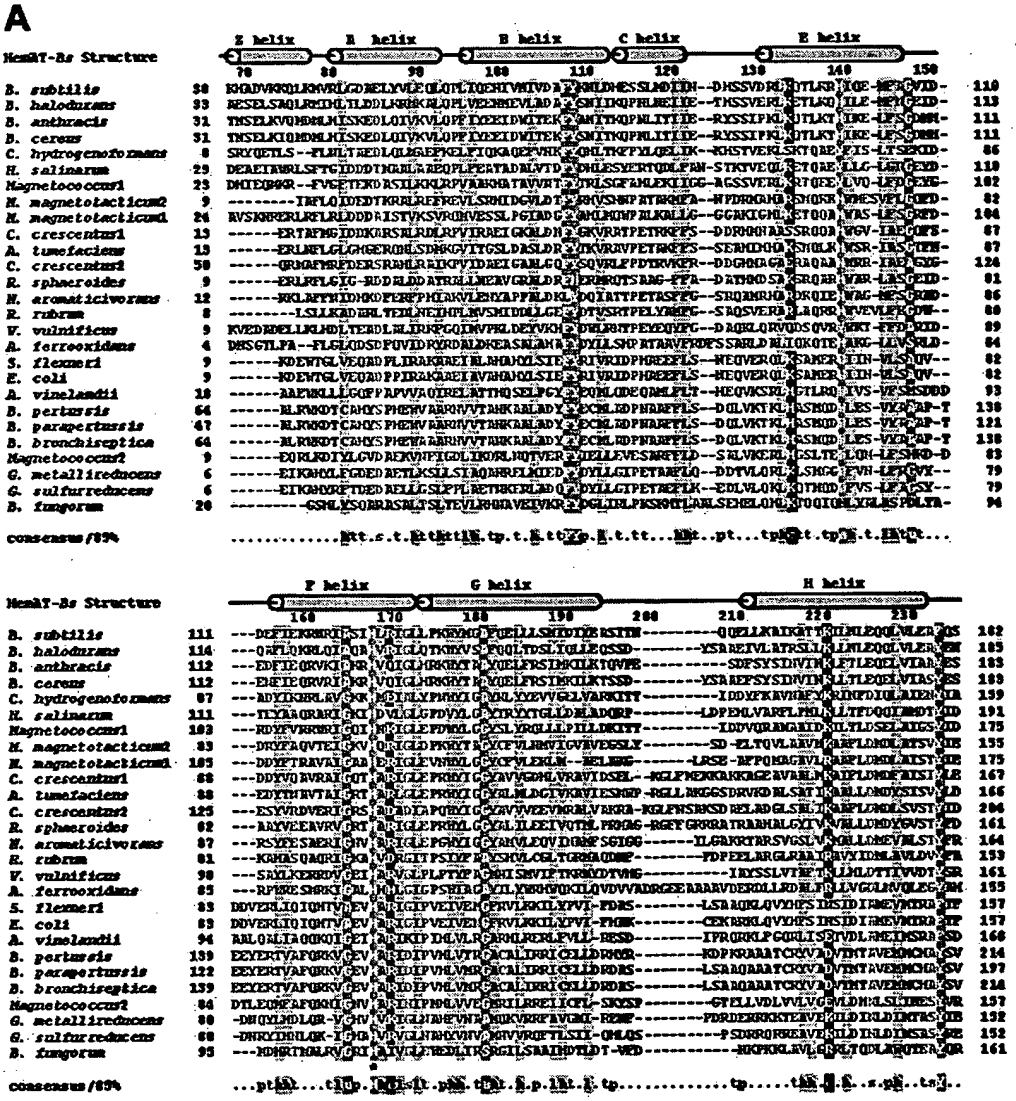

Fig. 1. Diversity of GCSs. The structural alignment (A) and the phylogenetic tree (B) of the GCS globin domain. A: The structural alignment of the globin domains from 27 GCSs was created in ClustalX and MegAlign and includes the 2D structure of the recent HemAT-*Bs* crystal structure (PDB ID: 1OR6) (personal communication) as a reference. The traditional helical assignments are maintained as helices A through H, with an additional Z helix at the N-terminus. The asterisk (*) indicates the conserved proximal histidine. Amino acid conservation has been based on an 85% consensus sequence and colors are assigned to amino acid groups as follows: charged (c, DEHKR) in white on blue background; polar (p, KRHEDQNST) in red; turn-like (t, ACDEGHKNPQRST) in green; bulky hydrophobic (h, ACLIVMHYFW) and aliphatic (l, LIVM) in yellow; aromatic (a, FHWY) in white on pink background; small (s, ACDGNPSTV) in purple; and tiny (u, AGS) in white on purple background. B: The phylogenetic tree is based on the alignment of part A of this figure with branches grouping according to transmitter type. Branches supported with bootstrap values > 5000 are indicated. Taxonomic listings for the GCS-containing organisms are listed with the organisms' names colored according to the type of transmitter domain. Pink, GAF:EAL; orange, unclassified; blue, ERERQR:GGDEF; purple, GGDEF:EAL; green, STAS; red, MCP or HAMP:MCP.

www.ebi.ac.uk/interpro). Various BLAST and PSI-BLAST searches were performed against the non-redundant database and the microbial database at the National Center for Biotechnology Information (http://www.ncbi.nih.gov/BLAST/). Transmembrane regions were identified by the algorithms TMHMM2 and DAS (http://www.cbs.dtu.dk/services/TMHMM-2.0/ and http://www.sbc.su.se/~miklos/DAS/).

2.4. Phylogenetic analyses

The distance tree was created using the neighbor-joining (ClustalX) method. Bootstraps (10000 replicates) were calculated directly in ClustalX. Trees were generated in TreeView and NJPlot (distributed with the ClustalX package) and further refined in Adobe Illustrator 10.

3. Results and discussion

An exhaustive heuristic search of the non-redundant protein database and (un)finished microbial genome database at NCBI yielded 27 GCSs. Criteria for identifying a putative GCS included a primary match with the globin domain followed by an accompanying transmitter domain(s). In addition, the length of the globin domain was taken into account as well as the presence of a proximal histidine. In almost all cases, a hydrophobic aromatic residue pair at the end of the B helix (usually Phe-Tyr) was also present. Secondary structure predicting algorithms and the 3D-PSSM fold-recognition server were used to support their inclusion into the family. Using (PSI)BLAST as the primary search algorithm, once a GCS was identified, it was added to the seed alignment. Since the GCS globin domains are highly divergent, each GCS sequence added to the growing alignment used as a (PSI)BLAST probe for additional candidates.

Neither the SMART database nor the manually curated Pfam-A dataset recognizes the GCS globin domain yet, though the automatically generated Pfam-B family 7730 has an incomplete and partially incorrect (on the basis of the above criteria) GCS globin domain dataset. Fig. 1A represents the alignment of the globin domain of all 27 GCSs. The resulting Neighbor-joining phylogenetic tree was created based on this alignment and is presented in Fig. 1B.

3.1. Biological heme-sensor classification

Using the identified functions of CooA, NPAS2, sGC, Dos, *Ax*PDEA1, FixL, and HemATs, all currently identified biological heme-based sensors can be classified as either aerotactic or gene regulating. Gene regulation is observed to occur via one of three different pathways: via protein–DNA interaction [2–6], via modulation of small-metabolite 2nd messengers [7–12], or by protein–protein interaction as in a transcription factor or regulator [13–16]. The resulting organization schema is illustrated in Fig. 2. GCSs are found in organisms with various physiological and metabolic systems: Gram-positive and Gram-negative, aerobic and anaerobic, oxic and anoxic phototrophs, and even a nitrogen fixer (*A. vinelandii*).

3.1.1. Aerotactic. HemATs are the only known heme-based aerotaxis sensors [17,18] and approximately half of the predicted GCSs are HemATs. Each possess an N-terminal globin domain and a C-terminal MCP-like domain. The original HemAT signaling domain was classified as an ~MCP [17]; however, additional HemATs exhibit a ~HAMP:MCP module. Such a combination is typical of transmitter regions of methyl-accepting chemotaxis proteins such as the *E. coli* serine receptor, Tsr, and hence these proteins may mediate aerotaxis as well. All HemATs are soluble proteins.

The aerotactic subfamily is predominantly Gram-negative α-Proteobacteria (nine proteins), but also includes the Firmicutes (five proteins) and one Archaea. In particular, the magnetotactic proteobacterium *M. magnetotacticum* possesses two aerotactic transducers, whereas *Magnetococcus* MC-1 cells possess only one. Magnetotaxis has been shown to work in conjunction with aerotaxis [22]. Though only a single Archaeal transducer has been found, this is not surprising since at least half of the sequenced Archaeal genomes do not contain recognizable taxis genes. Moreover, the representative sample size of the Archaeal genomes (one GCS out of 18 genomes ~6%) is miniscule compared to that of the bacterial genomes (26 GCSs out of 228 genomes ~11%).

3.1.2. Modulation of a 2nd messenger. Proteins possessing the GGDEF domain have been implicated in c-diGMP modulation [23] and eight such proteins were identified in this group, incorporating either the GGDEF domain or a GGDEF:EAL domain pair. Closer inspection of these proteins reveals another highly conserved domain centered between the N-terminal globin sensor and the C-terminal GGDEF domain. This new domain has been designated as ERERQR, after a conserved patch of residues (≥85% of five acidic, seven basic, 32 polar and 25 hydrophobic sites in a primarily alpha-helical and coiled structure, data not shown). *Af*GReg2M has the exact C-terminal domain organization as *Ec*Dos and *Ax*PDEA1 (~GGDEF:EAL), PDEs that inactivate the 2nd messengers cAMP and c-diGMP, respectively. The GCS from *B. fungorum* (*Bf*GReg) possesses a C-terminal

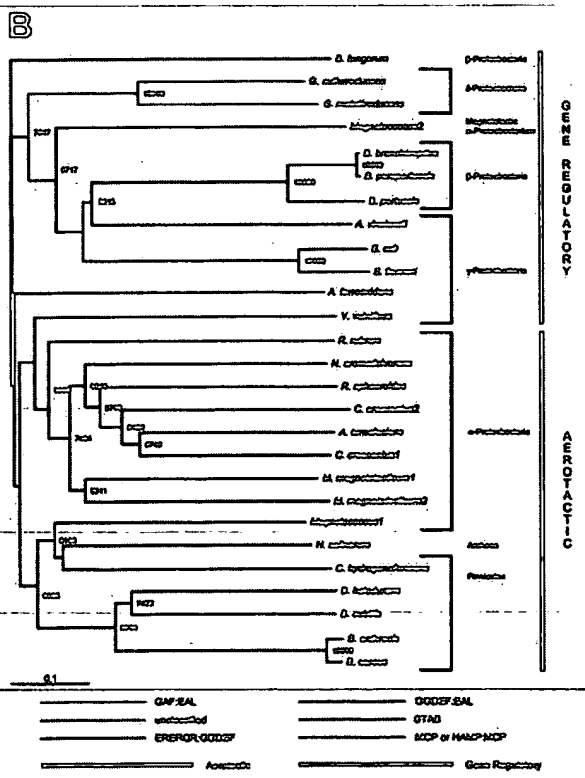

Fig. 1 (*Continued*).

Table 1
Source information and classification of GCSs

No.	Organism	Name	NCBI accession no.	Classification	SMART	Pfam	Taxonomy	Protein length	Other name
1	*Bacillus anthracis*	HemAT-*Ba*	NP_653892	Aerotactic	MA	MCP	Firmicutes	434	BA_0532
2	*Bacillus halodurans*	HemAT-*Bh*	NP_241371	Aerotactic	MA	MCP	Firmicutes	441	BH505
3	*Bacillus subtilis*	HemAT-*Bs*	NP_388919	Aerotactic	MA	MCP	Firmicutes	433	YhfV
4	*Bacillus cereus*	HemAT-*Bc*	NP_835085	Aerotactic	MA	MCP	Firmicutes	434	–
5	*Carboxydothermus hydrogenoformans*	HemAT-*Ch*	TIGR_129958	Aerotactic	MA	MCP	Firmicutes	251	–
6	*Halobacterium* sp. NRC-1	HemAT-*Hs*	NP_280321	Aerotactic	MA	MCP	Archaea	490	HtrX, HtB, Htr10
7	*Magnetospirillum magnetotacticum*	HemAT-*MmA*	ZP_00054774	Aerotactic	MA	MCP	α-Proteobacteria	444	Magn7582
8	*Magnetospirillum magnetotacticum*	HemAT-*MmB*	ZP_00054075	Aerotactic	MA	MCP	α-Proteobacteria	732	Magn6867
9	*Rhodobacter sphaeroides*	HemAT-*Rs*	ZP_00006252	Aerotactic	MA	MCP	α-Proteobacteria	371	Rsph2166
10	*Rhodospirillum rubrum*	HemAT-*Rr*	ZP_00014161	Aerotactic	MA	MCP	α-Proteobacteria	442	Rrub1164
11	*Agrobacterium tumefaciens*	HemAT-*At*	NP_354049	Aerotactic	HAMP-MA	HAMP-MCP	α-Proteobacteria	500	AGR_C_1888
12	*Caulobacter crescentus*	McpB	NP_419247	Aerotactic	HAMP-MA	HAMP-MCP	α-Proteobacteria	538	McpB
13	*Caulobacter crescentus*	McpM	NP_421120	Aerotactic	HAMP-MA	HAMP-MCP	α-Proteobacteria	556	McpM
14	*Novosphingobium aromaticivorans*	HemAT-*Na*	ZP_00095064	Aerotactic	HAMP-MA	HAMP-MCP	α-Proteobacteria	482	Saro2089
15	*Magnetococcus* sp. MC-1	HemAT-*Mg*	ZP_00043038	Aerotactic	HAMP-MA	HAMP-MCP	α-Proteobaceria	519	Mmc10749
16	*Magnetococcus* sp. MC-1	*Mg*GReg	ZP_00042662	Gene regulator (2nd messenger)	ERERQR:DUF1	ERERQR:GGDEF	α-Proteobaceria	467	Mmc10355
17	*Bordetella bronchiseptica*	*Bb*GReg	n/a	Gene regulator (2nd messenger)	ERERQR:DUF2	ERERQR:GGDEF	β-Proteobacteria	531	–
18	*Bordetella parapertussis*	*Bpa*GReg	n/a	Gene regulator (2nd messenger)	ERERQR:DUF3	ERERQR:GGDEF	β-Proteobacteria	514	–
19	*Bordetella pertussis*	*Bpe*GReg	n/a	Gene regulator (2nd messenger)	ERERQR:DUF4	ERERQR:GGDEF	β-Proteobacteria	531	–
20	*Escherichia coli*	*Ec*GReg	NP_287665	Gene regulator (2nd messenger)	ERERQR:DUF5	ERERQR:GGDEF	γ-Proteobacteria	460	YddV
21	*Azotobacter vinelandii*	*Av*GReg	ZP_00090857	Gene regulator (2nd messenger)	ERERQR:DUF6	ERERQR:GGDEF	γ-Proteobacteria	472	Avin2552
22	*Shigella flexneri* 2a str.301	*Sf*GReg	NP_707605	Gene regulator (2nd messenger)	ERERQR:DUF7	ERERQR:GGDEF	γ-Proteobacteria	381	YddV
23	*Acidithiobacillus ferrooxidans*	*Af*GReg	n/a	Gene regulator (2nd messenger)	DUF1-DUF2	GGDER:EAL	γ-Proteobacteria	880	–
24	*Burkholderia fungorum*	*Bf*GReg	ZP_00030046	Gene regulator (2nd messenger or Tmscon Reg)	GAF:DUF2	GAF-EAL	β-Proteobacteria	724	Bcep2859
25	*Vibrio vulnificus* CMCP6	*Vv*GReg	NP_762059	Gene regulator (2nd messenger)	STAS	STAS	γ-Proteobacteria	306	VV20073
26	*Geobacter sulfurreducens*	*Gs*GCS	n/a	*Unclassfiied*	–	–	δ-Proteobacteria	300	
27	*Geobacter metallireducens*	*Gm*GCS	ZP_00082251.1	*Unclassfiied*	–	–	δ-Proteobacteria	300	Gmet3020

Accompanying each GCS is the source organism, suggested naming convention along with any previous names, NCBI accession numbers (available except for those with genome sequencing in-progress), classification according to Fig. 2, domain topology as identified by SMART and Pfam, taxonomy and sequence length. Naming conventions for the GCSs are as follows: HemAT = heme-based aerotactic transducers; GReg = gene regulating.

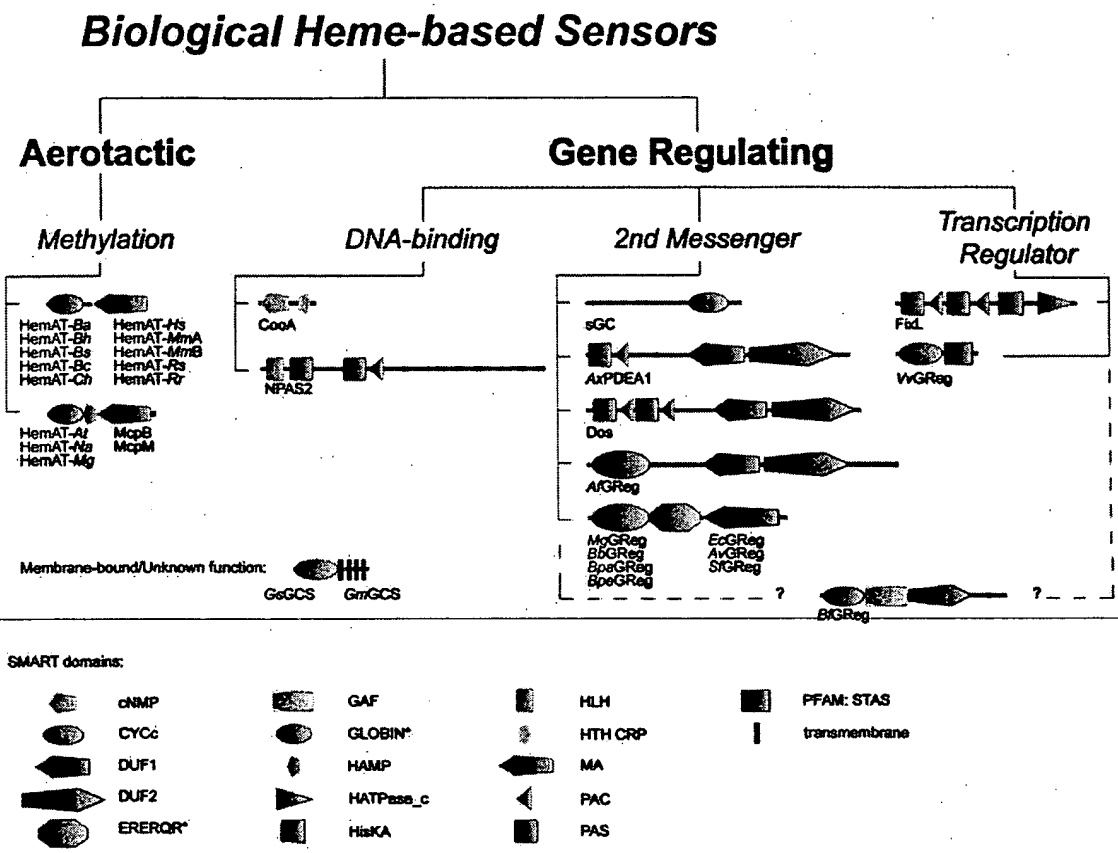

Fig. 2. Functional classification scheme of biological heme-based sensors. Heme-based sensors CooA, NPAS2, sGC, *Ax*PDEA1, Dos, FixL, and HemAT can be grouped according to their primary functions described in the literature. The GCSs are tentatively categorized according to this schema. *Bf*GReg is believed to be a gene regulator of either the 2nd messenger or transcription regulator class. No function could be assigned to the two membrane-bound *Geobacter* GCSs, *Gs*GCS and *Gm*GCS. Domains with an asterisks (*) indicate new domains not presently a part of the SMART database. See text and Table 1 for details.

GAF:EAL together with an additional PAS domain. Proteins possessing the GAF domain regulate small molecules like cAMP and cGMP and function in transcription [23–25].

3.1.3. Protein–protein interactions. *Vv*GReg from *V. vulnificus* possesses a C-terminal STAS (sulfate transporter and anti-σ factor antagonist) domain recognized by Pfam as an anti-anti-σ factor. Spore formation in *B. subtilis* is an example of such a regulated process utilizing σF (σ factor initiating prespore development), its antagonist SpoIIAB, and the anti-anti-σ factor, SpoIIAA. To our knowledge, *Vv*GReg is the first example of a globin domain with a transcriptional regulator. GCSs predicted to be involved in DNA binding have yet to be identified.

3.1.4. Unclassified GCS. Two GCSs identified in the strict anaerobic δ-Proteobacteria may be involved in sulfate/sulfur reduction. *Gs*GCS from *G. sulfurreducens* and *Gm*GCS from *G. metallireducens* exhibit a bundle of four transmembrane helices at C-terminal resemble either glutathione *S*-transferase (GST) or ferritin-like proteins. These are generally soluble proteins; however, a distinct microsomal membrane-bound GST family has been identified [26,27]. Both proteins are involved in cellular protection from toxicity of reactive oxygen species [28].

3.2. Phylogenetics of the GCSs

The phylogenetic tree (Fig. 1B) results in two interpretations: (1) there is a predisposition of bacterial lineages for particular signal-transducing elements, or (2) the globin domains are customized to function in concert with particular signal-transducing elements.

In the case of the GCS, a more evolved and ordered protein is built up from the less ordered components; namely, the ancestor globin, or *proto*globin, and the signaling domains. This higher ordered protein imparts a new function(s) to the host organism that allow descendants to thrive in environments that may not have been able to survive before. Rapid response to toxic oxygen or other highly reactive species that otherwise might quickly kill a microbe is a significant pressure to retain such a fusion protein. Within the tenet of the biological evolution, as atmospheric oxygen levels rose and eukaryotic cells evolved, the need for oxygen taxis may have diminished, resulting in the absence of such chimeric systems in the upper eukaryotes. There are three organisms that possess two GCSs: *C. crescentus*, *M. magnetotacticum*, and *Magnetococcus*. All four proteins in *C. crescentus* and *M. magnetotacticum* are HemATs and therefore it seems likely that they arose from gene duplication, i.e. they are paralogs. In contrast, the two GCSs from *Magnetococcus* perform different functions. One is a HemAT and the other, a predicted gene regulator. This indicates that each globin evolved independently with its particular signaling domain to reflect the observed diversity (Fig. 1B) and predicts the existence of the

protoglobin in more primitive organisms like the Archaea or the deeply branching photosynthetic bacteria.

4. Summary

The diversity of heme-based sensors in prokaryotes is predominantly globin based. The family of GCSs can be grouped into two subfamilies, the aerotactic and the gene regulating. Though approximately half of the GCSs fall into the gene-regulating subfamily, the HemATs are the only known heme-based sensors involved in aerotaxis. The GCSs form a family of proteins (Fig. 2) that, thus far, populate all but the direct DNA-binding sensors. Considering the diversity of the GCSs and that the flavohemoglobins are similar to the GCSs, we propose that this form of globin was particularly suited for forming multi-domain chimeric proteins with novel functions. We postulate that protoglobin was the predecessor to the chimeric GCS and should therefore be found in more ancient organisms, like the Archaea.

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